Oral pathology

Immune-mediated disorder

❖ Recurrent Aphthous Stomatitis (Recurrent Aphthous Ulcerations)

Recurrent aphthous stomatitis (RAS) is a common disease in humans. Within the oral cavity, RAS is the most common condition affecting the mucosal soft tissue.

Etiology:

The cause appears to be "different things in different people".

Although no single triggering agent is responsible, the mucosal destruction appears to represent a T cell–mediated immunologic reaction with production of tumor necrosis factor-alpha (TNF-α). This factor is a major inflammatory cytokine and assists in the ultimate targeting of the surface epithelium for destruction by cytotoxic T cells .

The initiating causes are elusive and most likely highly variable.

The following all have been reported to be responsible in certain subgroups of patients

- Allergies
- Genetic predisposition
- Hematologic abnormalities
- Hormonal influences
- Immunologic factors
- Infectious agents
- Nutritional deficiencies
- Smoking cessation
- Stress (mental and physical)
- Trauma

Systemic Disorders Associated with Recurrent Aphthous Stomatitis

- Bechtel syndrome
- Celiac disease
- Cyclic neutropenia
- Immunoglobulin A (IgA) deficiency
- Immunocompromised conditions, including human immunodeficiency virus (HIV) disease
- Inflammatory bowel disease
- MAGIC syndrome (mouth and genital ulcers with inflamed cartilage)

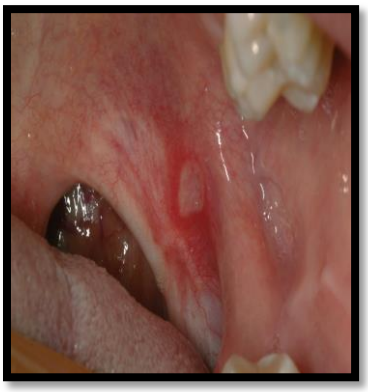
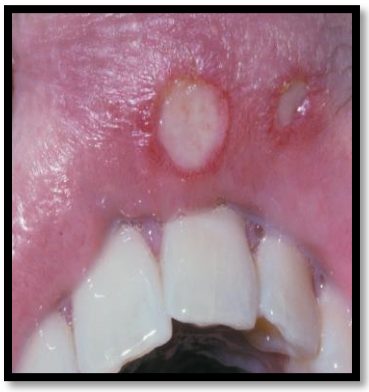
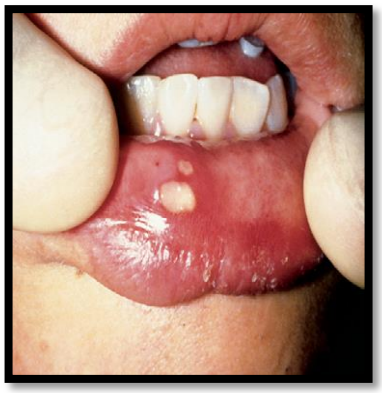
- Reactive arthritis

Clinical Features

Three forms of RAU have been recognized :

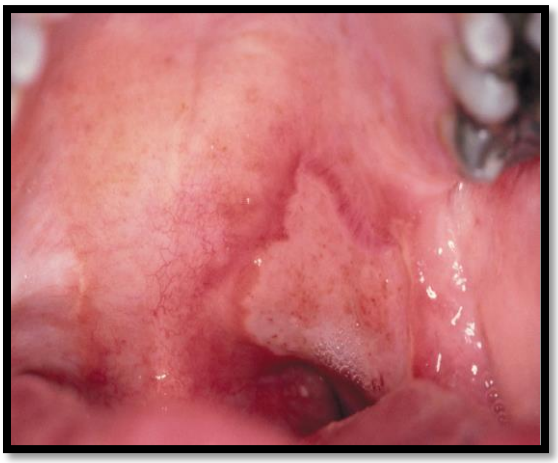
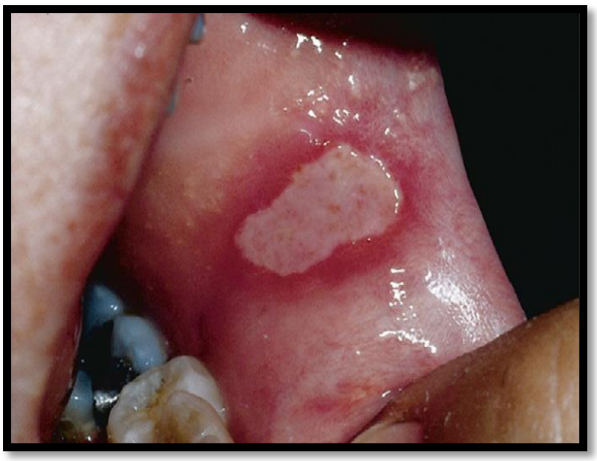
1. **Minor aphthous ulcer**

   Minor aphthos ulcers are the most commonly encountred form .Patients with minor aphthous ulcerations experience the fewest recurrences, and the individual lesions exhibit the shortest duration of the three variants. The ulcers arise almost exclusively on non-keratinized mucosa and may be preceded by an erythematous macule in association with prodromal symptoms of burning, itching, or stinging. The ulceration demonstrates a yellow-white, removable fibrinopurulent membrane that is encircled by an erythematous halo .
   Classically, the ulcerations measure between 3 and 10 mm in diameter, and heal without scarring in 7 to 14 days. From one to five lesions typically are present during a single episode, and the pain often is out of proportion for the size of the ulceration. The buccal and labial mucosae are affected most frequently, followed by the ventral surface of the tongue and mucobuccal fold, floor of the mouth, and soft palate.

2. **Major aphthous ulcer**

   Major aphthous ulcerations are larger than minor aphthae and demonstrate the longest duration per episode. The ulcerations are deeper than the minor variant, measure from 1 to 3 cm in diameter, take from 2 to 6 weeks to heal, and may cause scarring . The number of lesions varies from 1 to 10. Any oral surface area may be affected, but the labial mucosa, soft palate, and tonsillar fauces are involved most commonly .

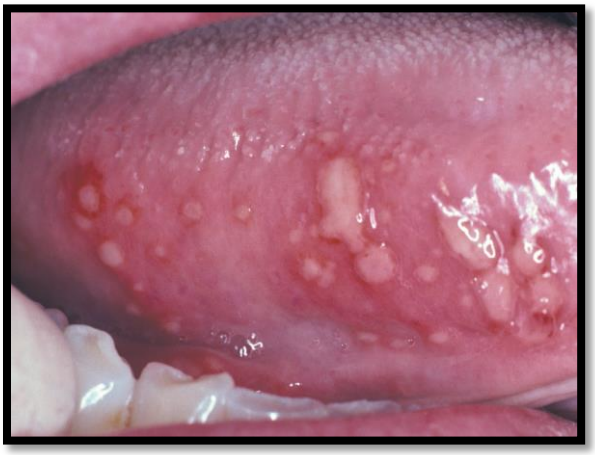
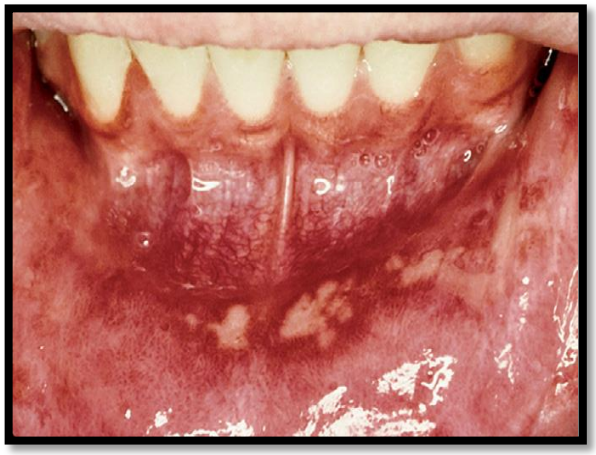



3. Herpetiform aphthous ulcer

Herpetiform aphthous ulcerations demonstrate the greatest number of lesions and the most frequent recurrences. The individual lesions are small, averaging 1 to 3 mm in diameter،with as many as 100 ulcers present in a single recurrence.

Because of their small size and large number, the lesions bear a superficial resemblance to a primary HSV infection. It is common for individual lesions to coalesce into larger irregular ulcerations .

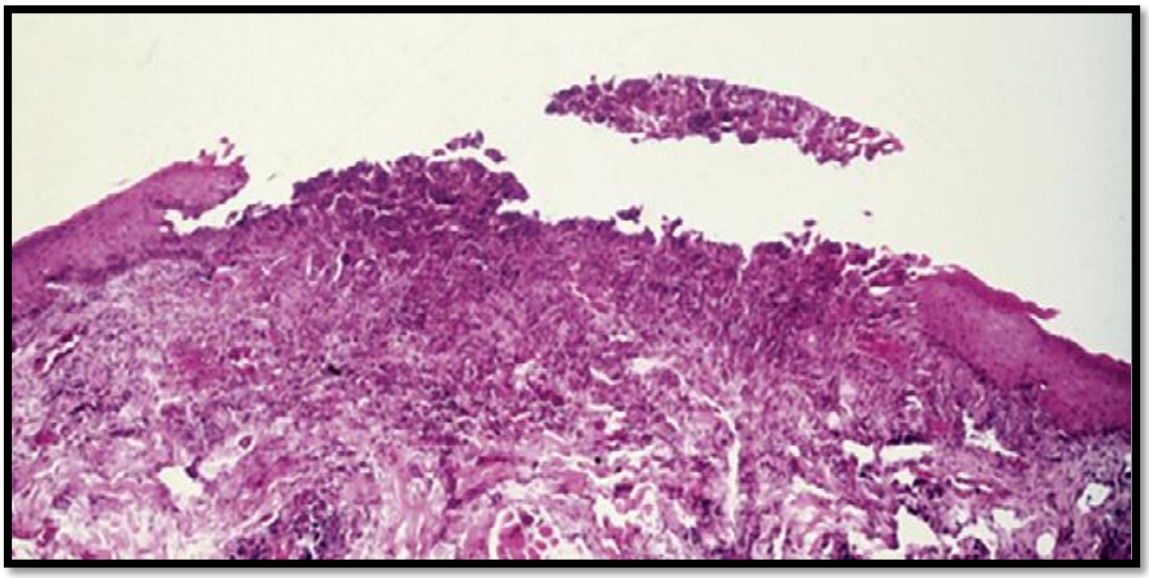
The ulcerations heal within 7 to 10 days, but the recurrences tend to be closely spaced. Although the non-keratinized, movable mucosa is affected most frequently.

Histopathology :

Biopsies is usually unnecessary because the diagnosis is evident clinically . The early ulcerative lesions demonstrate a central zone of ulceration, which is covered by a fibrinopurulent membrane. Deep to the area of ulceration, the connective tissue exhibits an increased vascularity and a mixed inflammatory cellular infiltrate that consists of lymphocytes, histiocytes, an polymorphonuclear leukocytes. The epithelium at the margin of the lesion

demonstrates spongiosis and numerous mononuclear cells in the basilar one-third. A band of lymphocytes intermixed with histiocytes is present in the superficial connective tissue and surrounding deeper blood vessels.



Treatment :

The patient's medical history should be reviewed for signs and symptoms of any systemic disorder .

Most patients with mild aphthosis receive either no treatment, or therapy with a number of anesthetics or protective bioadhesive products .

In patients with mild disease, the mainstay of therapy is the use of topical corticosteroids. Most patients with diffuse minor or herpetiform aphthae respond well to dexamethasone solution (0.5 mg/5 mL) used in a rinse-and-expectorate method.

Patients with localized ulcerations can be treated successfully with 0.05% augmented betamethasone dipropionate gel or 0.05% fluocinonide gel.

Major aphthous ulcerations are more resistant to therapy and the individual lesions may be injected with triamcinolone acetonide or covered with 0.05% clobetasol propionate gel . Triamcinolone tablets also can be dissolved directly over the lesions. In resistant cases, systemic corticosteroids may be required .

Widely accepted topical alternatives drugs include amlexanox paste, chlorhexidine , tetracycline oral suspension. Frequently mentioned systemic therapies include a number of immunomodulatory agents, such as colchicine, dapsone, pentoxifylline, and thalidomide.

Although laser ablation shortens the duration and decreases associated symptoms.

Chemical cautery with silver nitrate continues to be suggested as an effective therapy.

❖ Behçet's syndrome

Behçet syndrome is an uncommon complex multisystem condition that is diagnosed by means of clinical criteria. The main features as consisting of oral and genital aphthae, pustular vasculitic cutaneous lesions, and ocular and GI vasculitic lesions.

The cause of Behçet syndrome is unknown. Immune factors, infectious agents, and immune effector mechanisms have been implicated where represent an abnormal immune process triggered by an infectious or environmental antigen in a genetically predisposed individual.

Clinical Features:

Behçet syndrome usually arises in the third and fourth decades . Men exhibit a slightly increased prevalence .

Virtually all affected patients demonstrate oral lesions 100% , genital ulcerations (75 % of cases) and eye lesions . Other less frequently associated features include cutaneous lesions, arthritis, uveitis، thrombophlebitis, gastrointestinal manifestations, and central nervous system (CNS) involvement.

The oral lesions are similar to aphthous ulcerations and demonstrate the same duration and frequency. All three forms of oral aphthous stomatitis may be seen.

The genital lesions in males, approximately 90% of the lesions involve the scrotum, whereas those in females are most frequent on the vulva, vagina, or uterine cervix. perianal involvement .

Ocular involvement occurs in up to 70% of the cases and is more frequent and severe in males. The most common findings are posterior uveitis, conjunctivitis, corneal ulceration, and arteritis. The most common secondary ocular complications are cataracts, glaucoma.

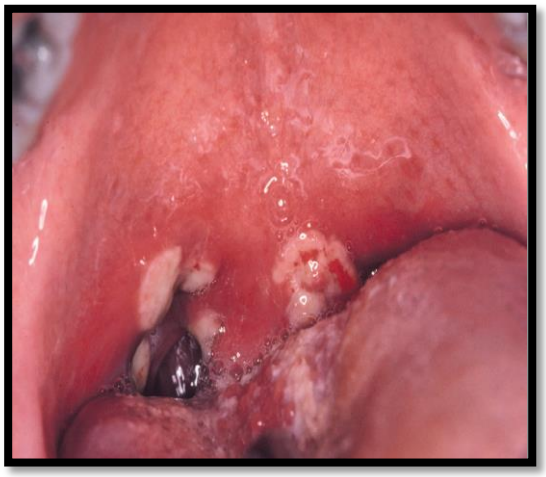
Common cutaneous lesions include erythematous papules, pustules acneiform eruptions, and erythema nodosum–like lesions .

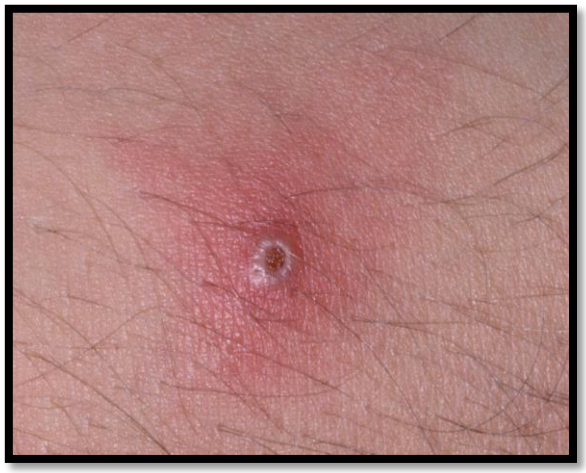
Arthritis is one of the more common minor manifestations of the disease and is usually self-limiting and non-deforming.

Although the vascular disease may involve arteries, veins are affected more frequently and present as superficial and deep thrombophlebitis.

Gastrointestinal disease is variable and includes abdominal pain, anorexia, diarrhea, dyspepsia, and vomiting.

CNS involvement is not common but, when present, is associated with a poor prognosis.





Diagnosis :

Criteria for the Diagnosis of Behçet Disease:

- Recurrent oral ulceration ⟶ Minor, major, or herpetiform aphthae

Plus two of the following:

- Recurrent genital ulcerations
- Eye lesions Anterior or posterior uveitis, cells in vitreous on slit-lamp examination, or retinal vasculitis.
- Skin lesions Erythema nodosum, pseudofolliculitis or papulopustular lesions, or acneiform nodules noted in postadolescent patients not receiving corticosteroids
- Positive pathergy test Read by physician at 24 to 48 hours.

Histopathology:

The histopathologic features are not specific for Behçet syndrome and can be seen in many disorders, including aphthou stomatitis. The pattern most frequently seen is called leukocytoclastic vasculitis. The ulceration is similar in appearance to that seen in aphthous stomatitis, but the small blood vessels classically demonstrate intramural invasion by neutrophils، karyorrhexis of neutrophils, extravasation of red blood cells, and fibrinoid necrosis of the vessel wall.

Treatment :

No single medication is universally effective with variable responses seen in different groups of patients. Systemic medications include azathioprine, colchicine, corticosteroids، cyclosporine, dapsone, interferon-α, methotrexate, pentoxifylline, thalidomide, and anti-TNF-α medications .

The oral and genital ulcerations typically respond well to potent topical or intralesional corticosteroids or topical tacrolimus.

❖ Erythema Multiforme

Erythema multiforme (EM) is an inflammatory disease of immune origin that affects the skin and mucous membranes and is a blistering, ulcerative mucocutaneous condition. It has been divided into two subtypes : Erythema multiforme minor and Erythema multiforme major.

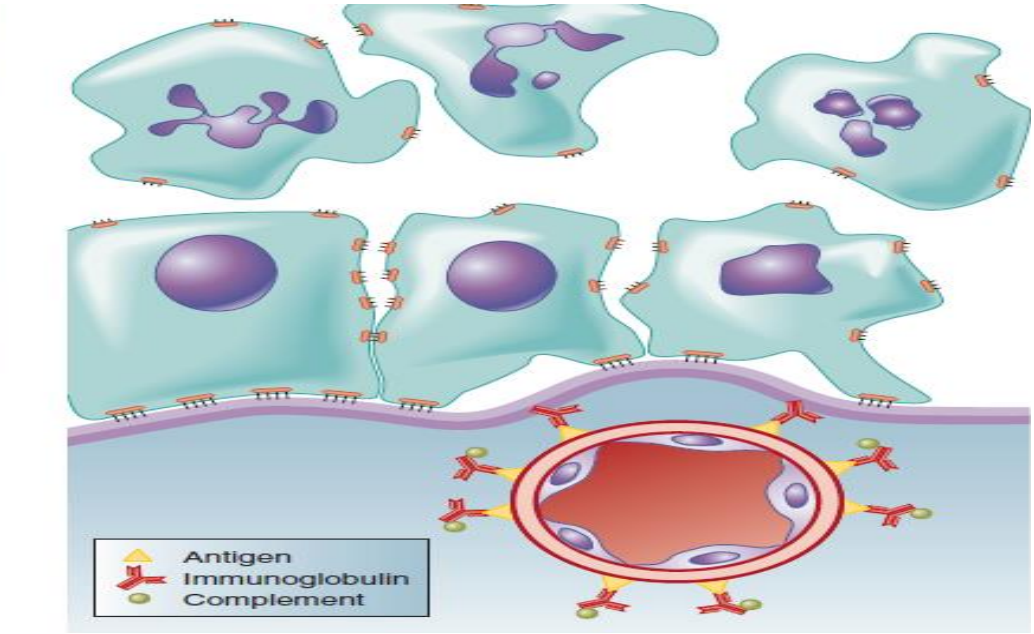
The common precipitating factors are :

1. Infections such as herpes simplex, mycoplasma pneumonia.
2. Drugs (mostly sulfas, penicillin، Dilantin, barbiturates and iodines)
3. GI conditions (Crohn disease and ulcerative colitis).
4. Conditions such as malignancy, radiation therapy, and recent vaccination.

The pathogenesis of EM is mostly unknown. Research has identified circulating immune-related complexes that appear after patients have encountered some infections and after allergic reactions to medications.

Antibodies form against an exogenous antigen and the complex circulates in the blood being filtered in the walls of blood vessels; there they cause a vasculitis , which results in small areas of thrombosis and ischemic necrosis. The resulting skin

and mucosal reactions range from a mild erythema to widespread necrosis with sloughing of the epithelial layer, depending on the intensity of the immune response to the antigen.

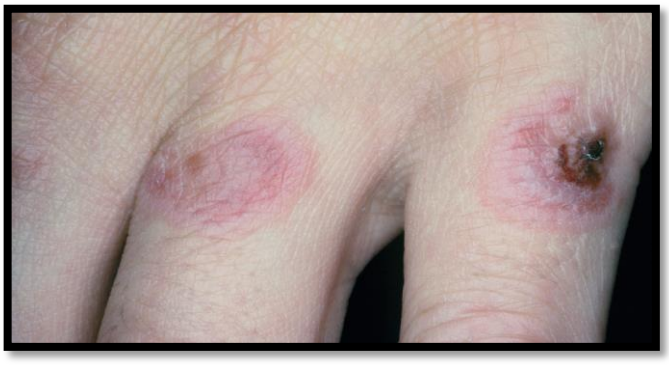


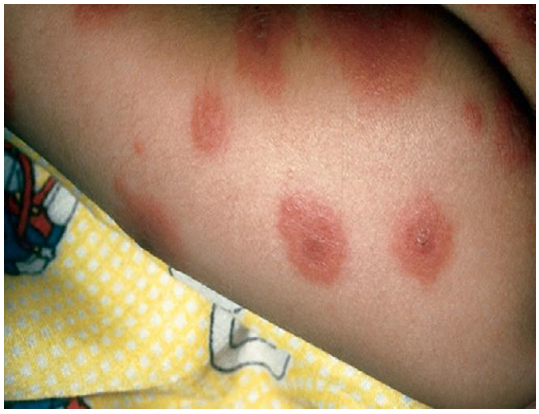
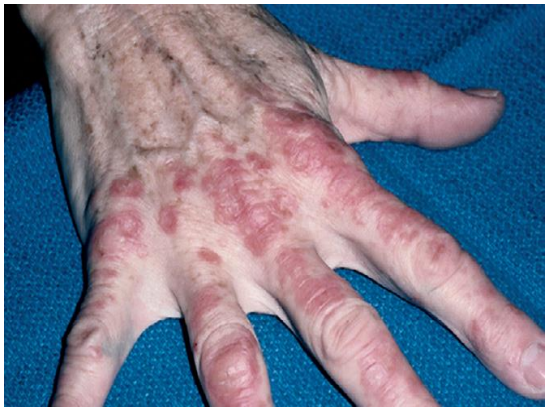
Clinical Features:

Erythema multiforme typically has an acute onset and usually affects young adults with a slight female predilection . Prodromal symptoms are often present and include fever, malaise، headache, cough, and sore throat, occurring approximately 1 week before onset.

Erythema multiforme minor, usually begin with the development of slightly elevated, round, dusky-red patches on the skin of the extremities. These lesions may have a variety of appearances. Some of these skin lesions develop features that are highly characteristic for the disease. These lesions appear as concentric circular erythematous rings resembling a target or bull's-eye (target lesions) .

In more severe cases, these may evolve into bullae with necrotic centers.



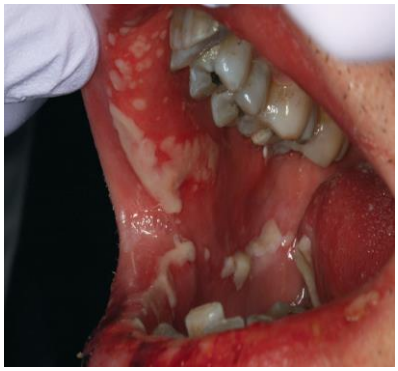
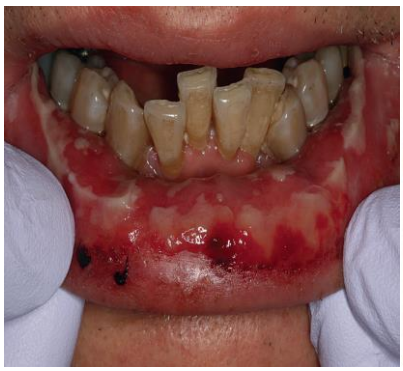
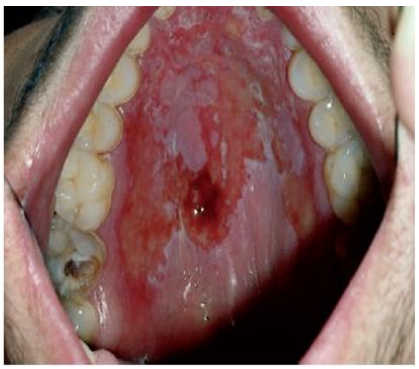



The oral cavity is the most frequently involved mucosal site, although the conjunctival, genitourinary, and respiratory mucosa also may be affected.

The oral lesions begin as erythematous patches that undergo epithelial necrosis and evolve into large, shallow erosions and ulcerations with irregular borders . Hemorrhagic crusting of the vermilion zone of the lips is common . Sometimes patients are dehydrated because they are unable to ingest liquids as a result of mouth pain.

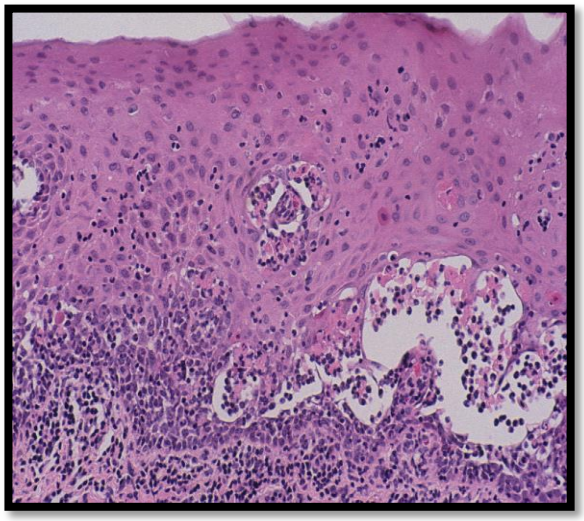
The ulcerations often have a diffuse distribution. The lips، labial mucosa, buccal mucosa, tongue, floor of the mouth، and soft palate are the most common sites of involvement. Usually, the gingivae and hard palate are relatively spared.

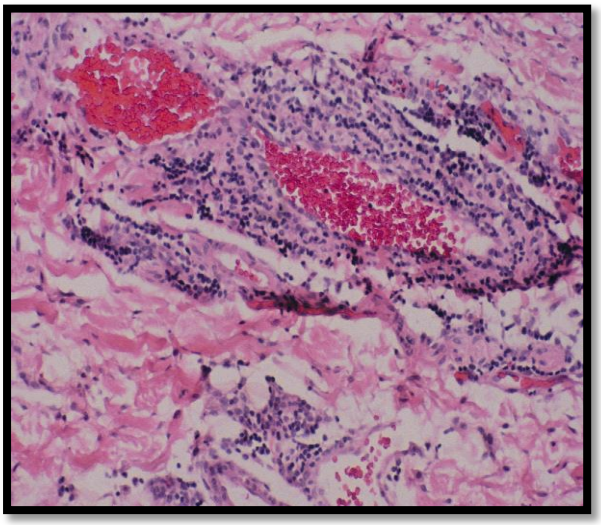
Erythema Multiforme Major their diagnosis can be made if two or more mucosal sites are affected in conjunction with widespread skin lesions. In most cases the oral mucosa is involved in addition to either the ocular or genital mucosae. With severe ocular involvement, scarring symblepharon formation may occur, similar to that in cicatricial pemphigoid .

Histopathology:

Histopathologic examination is not pathognomonic. Subepithelial or intraepithelial vesiculation may be seen in association with necrotic basal keratinocytes . A mixed inflammatory infiltrate is present, consisting of lymphocytes, neutrophils, and often eosinophils. Sometimes these cells are arranged in a perivascular orientation .





Treatment:

The disease is self-limiting, usually lasting 2 to 6 weeks . Treatment in mild cases is symptomatic and consists of antihistamines, analgesics, and antipyretics combined with oral rinses of antihistamine or the use of a topical steroid . If a causative drug is identified or suspected, then it should be discontinued immediately.

If the patient is dehydrated as a result of an inability to eat because of oral pain, then IV rehydration may be necessary along with topical anesthetic agents to decrease discomfort.

If disease is triggered by herpes simplex, then continuous oral acyclovir or valacyclovir therapy can prevent recurrences.

❖ Stevens-johnson syndrome and Toxic epidermal necrolysis

In the past, many dermatologists considered Stevens- Johnson syndrome and toxic epidermal necrolysis to represent the most severe end of the erythema multiforme but now is consider as separated entity . Although the inciting event in erythema multiforme is usually a herpes virus infection، Stevens-Johnson syndrome and toxic epidermal necrolysis are almost always triggered by drug exposure. Recent studies

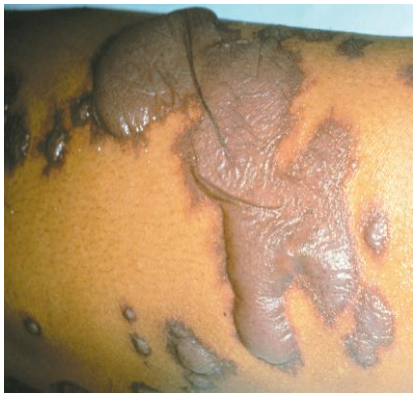
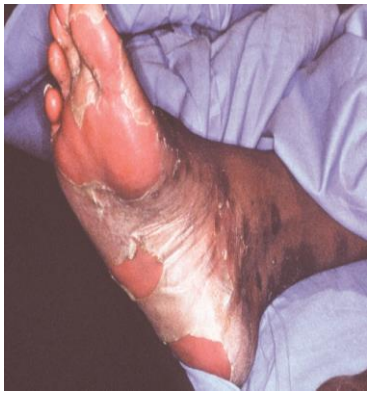
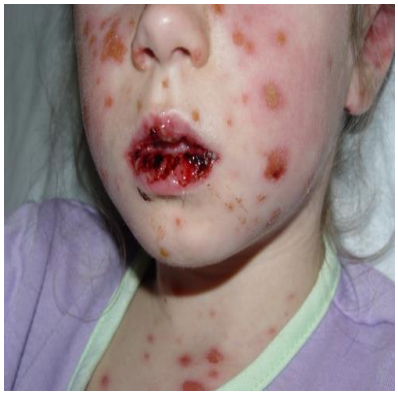
have shown that the damage to the epithelium is due to increased apoptosis of the epithelial cells, and several mechanisms have been postulated to account for this phenomenon.

Clinical Features:

The difference between Stevens-Johnson syndrome and toxic epidermal necrolysis is the degree of skin involvement، with Stevens-Johnson syndrome having less than 10% of the body surface affected by lesions, and toxic epidermal necrolysis having more than 30% involvement.

In contrast to Stevens-Johnson syndrome, which is usually seen in younger patients, toxic epidermal necrolysis tends to occur in people over 60 years of age. A female predilection is observed. These patients usually have flu-like prodromal signs and symptoms, including fever, malaise, sore throat, headache، and loss of appetite.

Within a few days, skin lesions begin to develop, but unlike erythema multiforme, the cutaneous lesions of Stevens-Johnson syndrome and toxic epidermal necrolysis initially appear on the trunk, presenting as erythematous macules (completely flat). Within 1 to 14 days، however, sloughing of the skin and flaccid bullae develop. If the patient survives، then the cutaneous process resolves in 3 to 5 weeks؛ however, oral lesions may take longer to heal, and significant residual ocular damage is evident in half of the patients.

Treatment :

Most identifying and immediately discontinuing any drug that might be initiating the condition. Management of patients of these lesions in the burn unit of the hospital is recommended.

❖ Lupus Erythematosus

Lupus erythematosus (LE) is a classic example of an immunologically mediated condition, and is the most common of the so-called collagen vascular or connective tissue diseases . It may exhibit any one of several clinicopathologic forms.

Systemic lupus erythematosus (SLE) is a serious multisystem disease with a variety of cutaneous and oral manifestations. There is an increase in the activity of the humoral limb (B lymphocytes) of the immune system in conjunction with abnormal function of the T lymphocytes. Although genetic factors probably play a role in the pathogenesis of SLE, the precise cause is unknown. Undoubtedly, interplay between genetic and environmental factors occurs.

Chronic cutaneous lupus erythematosus (CCLE) may represent a different, but related, process. It primarily affects the skin and oral mucosa, and the prognosis is good.

Subacute cutaneous lupus erythematosus (SCLE) is a third form of the disease, which has clinical features intermediate between those of SLE and CCLE.

Clinical Features:

1. **Systemic Lupus Erythematosus**

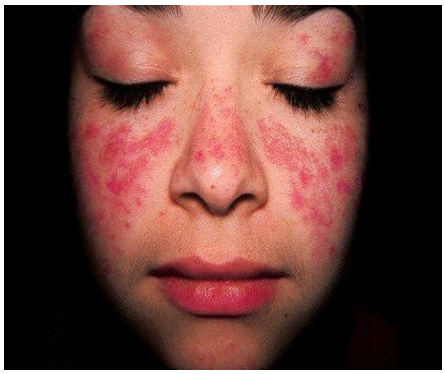
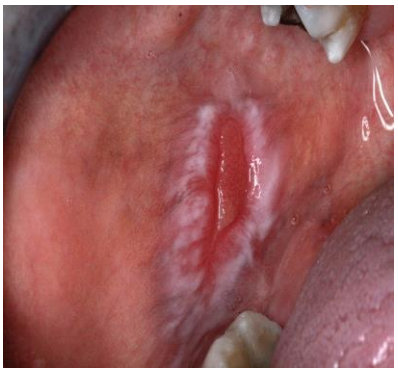
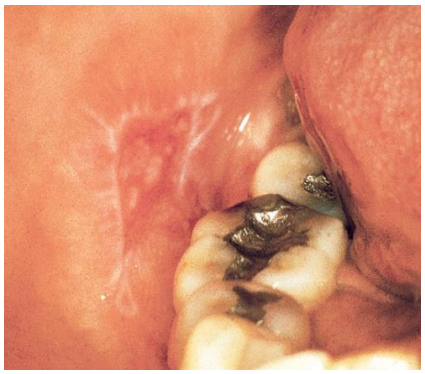
SLE can be a very difficult disease to diagnose in its early stages because it often appears in a nonspecific, vague fashion, frequently with periods of remission or disease inactivity. Women are affected nearly 8 to 10 times more frequently than men. The average age at diagnosis is 31 years.

Common findings include fever, weight loss, arthritis، fatigue, and general malaise. In 40% to 50% of affected patients, a characteristic rash, having the pattern of a butterfly، develops over the malar area and nose ,typically sparing the nasolabial folds. Sunlight often makes the lesions worse.

The kidneys are affected in approximately 40% to 50% of SLE patients. This complication may ultimately lead to kidney failure; thus it is typically the most significant aspect of the disease.

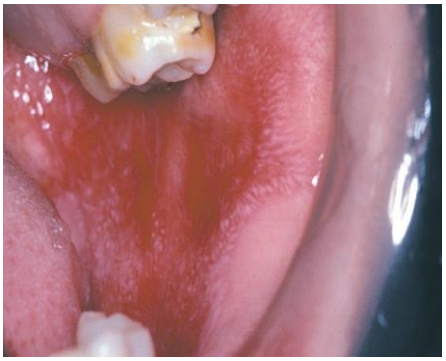
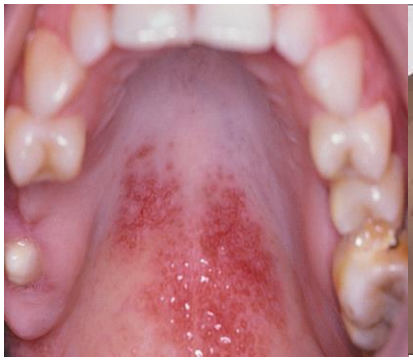
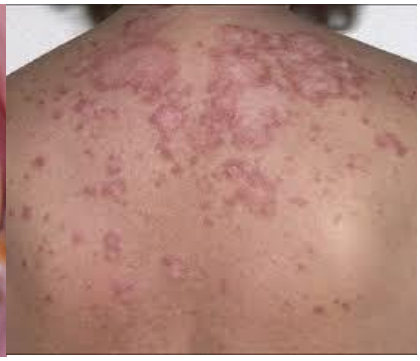
Cardiac involvement is also common, with pericarditis being the most frequent complication.

Oral lesions of SLE develop in 5% to 25% of these patients, although some studies indicate prevalence as high as 40%. The lesions usually affect the palate, buccal mucosa، and gingivae. Sometimes they appear as lichenoid areas, but they may also look nonspecific or even somewhat granulomatous . Involvement of the vermilion zone of the lower lip (lupus cheilitis) is sometimes seen. Varying degrees of ulceration, pain, erythema, and hyperkeratosis may be present. Other oral complaints such as xerostomia، stomatodynia, candidiasis, periodontal disease, and dysgeusia have been described, but the direct association of these problems with SLE remains to be proven.

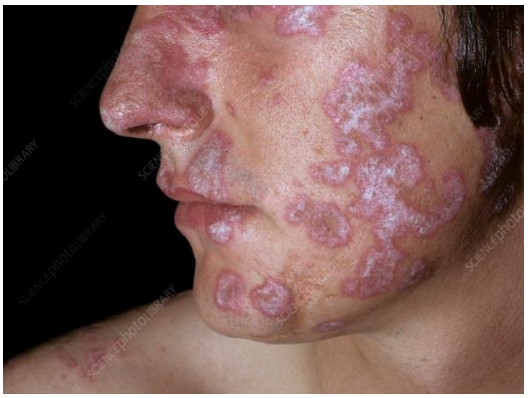
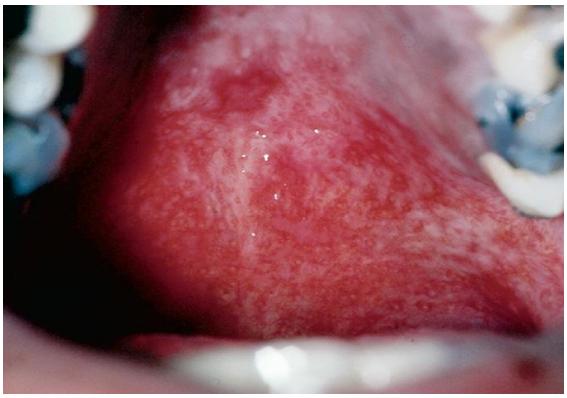
2. Chronic Cutaneous Lupus Erythematosus

Patients with CCLE usually have few or no systemic signs or symptoms, with lesions being limited to skin or mucosal surfaces. The skin lesions of CCLE most commonly present as discoid lupus erythematosus. They begin as scaly, erythematous patches that are frequently distributed on sun exposed skin, especially in the head and neck area . Patients may indicate that the lesions are exacerbated by sun exposure. With time, the lesions may heal spontaneously in one area, only to appear in another area. The healing process usually results in cutaneous atrophy with scarring and hypopigmentation or hyperpigmentation of the resolving lesion. In most cases the oral manifestations of CCLE essentially appear clinically identical to the lesions of erosive lichen planus. Unlike the oral lesions of lichen planus, however، the oral lesions of CCLE seldom occur in the absence of skin lesions. An ulcerated or atrophic, erythematous central zone, surrounded by white, fine, radiating striae, characterizes the oral lesion of CCLE . Sometimes the erythematous, atrophic central region of a lesion may show a fine stippling of white dots. As with erosive lichen planus , the ulcerative and atrophic oral lesions of CCLE may be painful, especially when exposed to acidic or salty foods.

3. Subacute Cutaneous Lupus Erythematosus

Patients with SCLE have clinical manifestations intermediate between those of SLE and CCLE. The skin lesions are the most prominent feature of this variation. They are characterized by photosensitivity and are, therefore, generally present in sun-exposed areas. These lesions do not show the induration and scarring seen with the skin lesions of CCLE. Oral lesions similar to those of CCLE have been described in this variant of lupus as well , most patients will have arthritis or musculoskeletal problems.

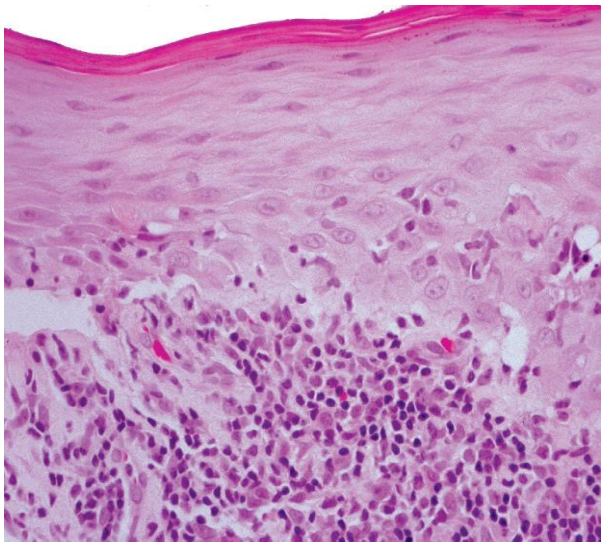



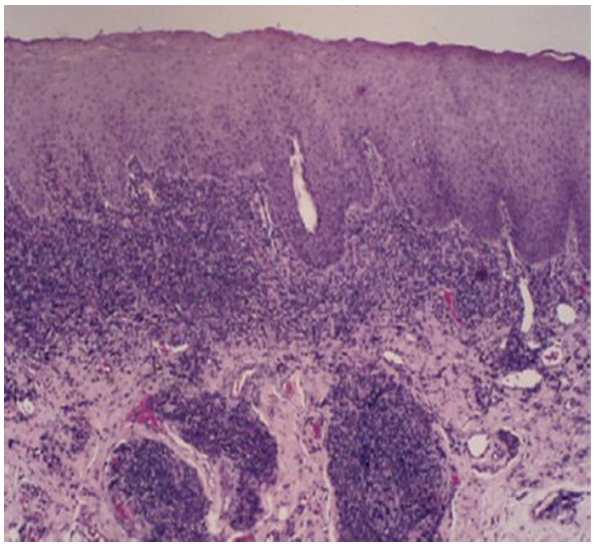
Histopathology;

The histopathologic features of the skin and oral lesions of the various forms of LE show some features in common but are different enough to warrant separate discussions. The skin lesions of CCLE are characterized by hyperkeratosis، often displaying keratin packed into the openings of hair follicles (“follicular plugging”). In all forms of LE، degeneration of the basal cell layer is frequently observed، and the underlying connective tissue supports patchy to dense aggregates of chronic inflammatory cells .

In the deeper connective tissue, the inflammatory infiltrate often surrounds the small blood vessels.

The oral lesions demonstrate hyperkeratosis, alternating atrophy and thickening of the spinous cell layer, degeneration of the basal cell layer, and subepithelial lymphocytic infiltration. These features may also be seen in oral lichen planus; however, the two conditions can usually distinguished by the presence in LE of patchy deposits of a periodic acid-Schiff (PAS)-positive material in the basement membrane zone, subepithelial edema (sometimes to the point of vesicle formation), and a more diffuse, deep inflammatory infiltrate, often in a perivascular orientation. Some authorities, however, feel that differentiating lichen planus from LE is best done by direct immunofluorescence studies or histopathologic examination of the cutaneous lesions.





Diagnosis:

In addition to the clinical and microscopic features, a number of additional immunologic studies may be helpful in making the diagnosis of LE.

1. Direct immunofluorescence testing of lesional tissue shows deposition of one or more immunoreactants (usually IgM, IgG, or C3) in a shaggy or granular band at the basement membrane zone.
2. Direct immunofluorescence testing of clinically normal skin of SLE patients often shows a similar deposition of IgG, IgM, or complement components. This finding is known as a **positive lupus band test**.

3. Evaluation of serum obtained from a patient with SLE shows various immunologic abnormalities. Approximately 95% of these patients have antibodies directed against multiple nuclear antigens (i.e., antinuclear antibodies [ANAs]).
4. Antibodies directed against double stranded DNA are noted in 70% of patients with SLE, and these are more specific for the disease.
5. Another 30% of patients show antibodies directed against Sm , a protein that is complexed with small nuclear RNA. This finding is very specific for SLE.

Treatment :

Patients with SLE should avoid excessive exposure to sunlight because UV light may precipitate disease activity. Mild active disease may be effectively managed using NSAIDs combined with antimalarial drugs, such as hydroxychloroquine.

For more severe, acute episodes that involve arthritis، pericarditis, thrombocytopenia, or nephritis, systemic corticosteroids are generally indicated; these may be combined with other immunosuppressive and immunomodulating agents. If oral lesions are present, they typically respond to the systemic therapy.

As with SLE patients, patients with CCLE should avoid excessive sunlight exposure. Because most of the manifestations of CCLE are cutaneous, topical corticosteroids are often reasonably effective. For cases that are resistant to topical therapy, systemic antimalarial drugs، immunosuppressive drugs, immunomodulating drugs, or low-dose thalidomide may produce a response. Topical corticosteroids are also helpful in treating the oral lesions of CCLE.

Vesiculobullous Lesions

Several conditions discussed in this lecture are the result of inappropriate production of antibodies by the patient (autoantibodies).

These autoantibodies are directed against various constituents of the molecular apparatus that hold epithelial cells together or that bind the surface epithelium to the underlying connective tissue. The ensuing damage produced by the interaction of these autoantibodies with the host tissue is seen clinically as a disease process,

often termed an immunobullous disease. Because each disease is characterized by production of specific types of autoantibodies، identification of the antibodies and the tissues against which they are targeted is important diagnostically. The two techniques that are widely used to investigate the immunobullous diseases are

1- Direct immunofluorescence

2- Indirect immunofluorescence studies.

❖Pemphigus

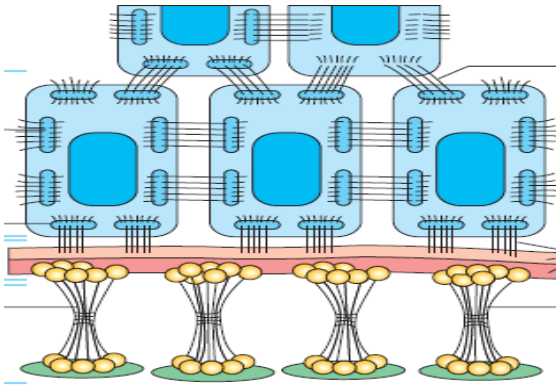
The condition known as pemphigus represents four related diseases of an autoimmune origin:

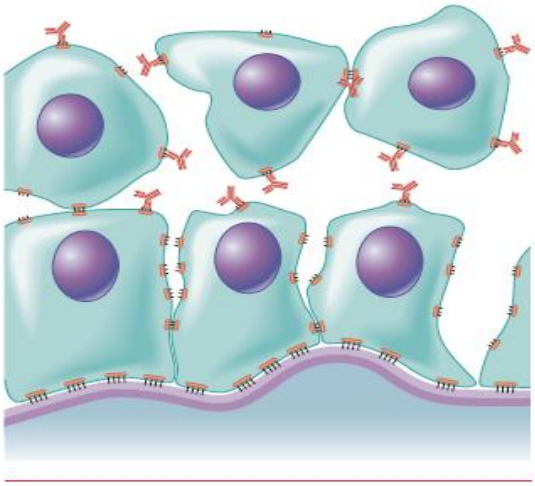
1. Pemphigus vulgaris
2. Pemphigus vegetans
3. Pemphigus erythematosus
4. Pemphigus foliaceus

Only the first two of these affect the oral mucosa, and the discussion is limited to pemphigus vulgaris. Pemphigus vegetans is rare; most authorities now feel it represents simply a variant of pemphigus vulgaris.

Pemphigous Vulgaris

Pemphigus vulgaris (PV) are a group of mucocutaneous diseases characterized by epithelial desquamation caused by abnormal production for unknown reasons of autoantibodies that attack the desmosome of the intercellular cohesive system. The loss of adhesion occurs between the cells located in the zone above the basal cell layer and a result of this immunologic attack on the desmosomes, a split develops within the epithelium, causing a blister (suprabasilar bullous formation) . Destruction of the adhesive factors of the suprabasila spinous cells is referred to as acantholysis.



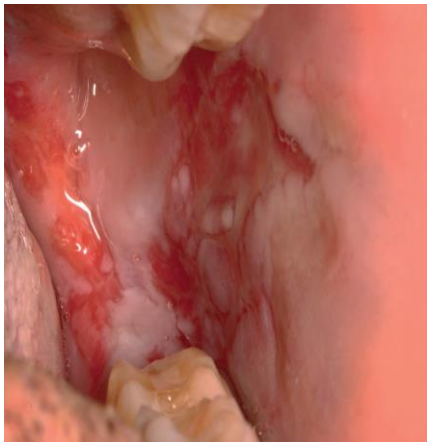
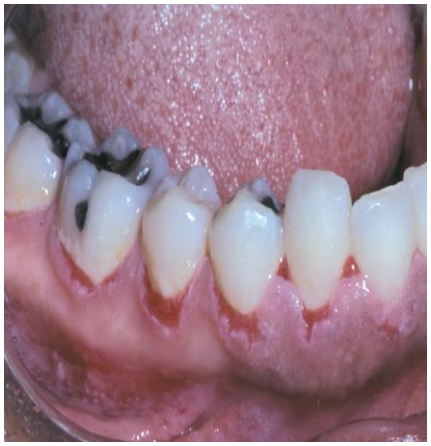
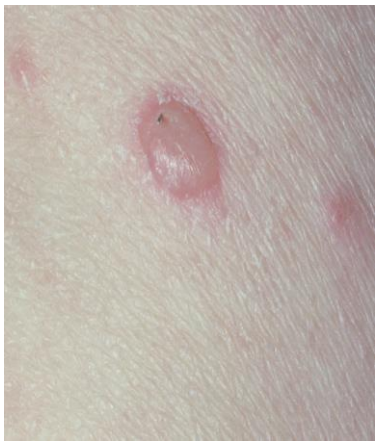


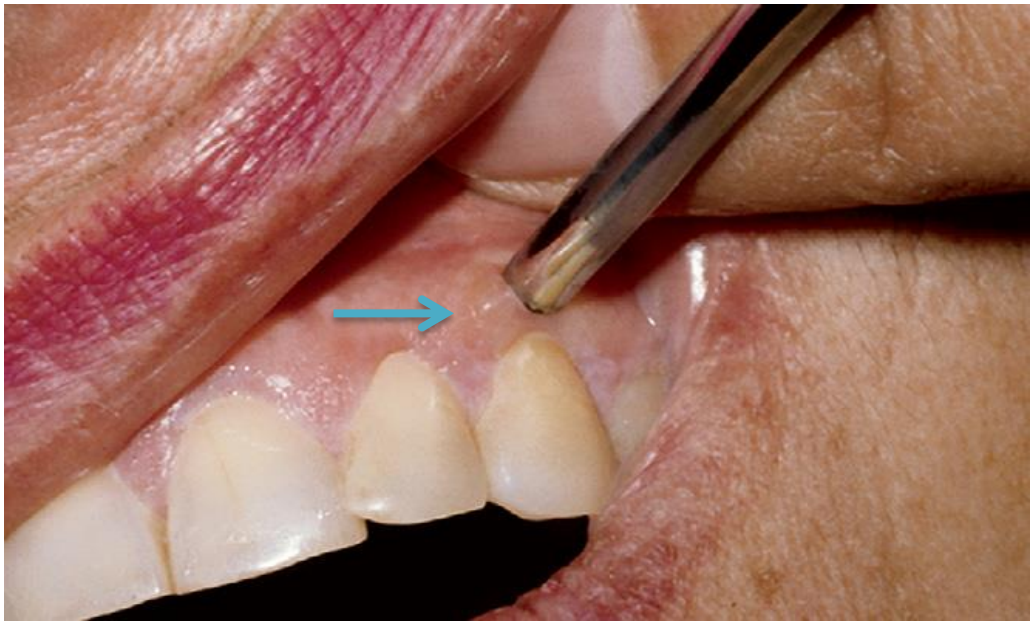
CLINICAL FEATURES:

The initial manifestations of pemphigus vulgaris often involve the oral mucosa, typically in adults. The average age at diagnosis is 50 years. The condition seems to be more common in persons of Mediterranean، South Asian, or Jewish heritage.

Patients usually complain of oral soreness, and examination shows superficial, ragged erosions and ulcerations distributed haphazardly on the oral mucosa . Such lesions may affect virtually any oral mucosal location, although the palate, labial mucosa, buccal mucosa، ventral tongue, and gingivae are often involved. Patients rarely report vesicle or bulla formation intraorally, and such lesions can seldom be identified by the examining clinician،probably because of early rupture of the thin, friable roof of the blisters. More than 50% of the patients have oral mucosal lesions before the onset of cutaneous lesions, sometimes by as much as 1 year or more. Eventually, however، nearly all patients have intraoral involvement. The skin lesions appear as flaccid vesicles and bullae that rupture quickly, usually within hours to a few days, leaving an erythematous, denuded surface. Infrequently ocular involvement may be seen, usually appearing as bilateral conjunctivitis. Unlike cicatricial pemphigoid, the ocular lesions of pemphigus typically do not cause scarring and symblepharon formation .

A characteristic feature of pemphigus vulgaris is that a bulla can be induced on normal-appearing skin if firm lateral pressure is exerted. This is called a positive Nikolsky sign.



Nikolsky's sign

Histopathologic Features:

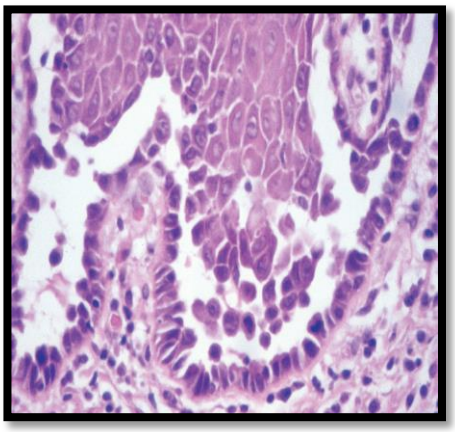
Biopsy specimens of perilesional tissue show characteristic intraepithelial separation, which occurs just above the basal cell layer of the epithelium . Sometimes the entire superficial layers of the epithelium are stripped away، leaving only the basal cells, which have been described as resembling a “row of tombstones.”

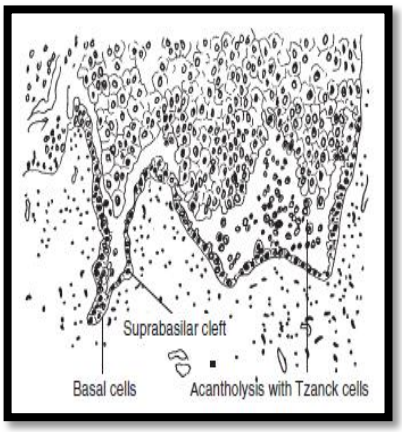
The cells of the spinous layer of the surface epithelium typically appear to fall apart،

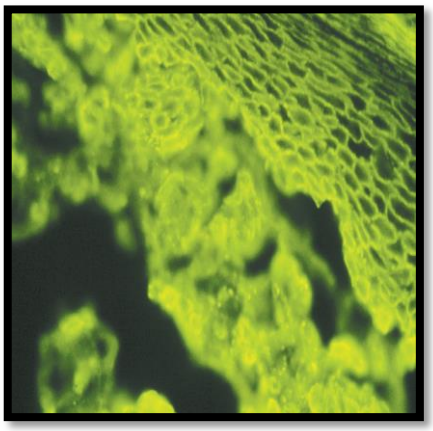
a feature that has been termed acantholysis, and the loose cells tend to assume a rounded shape . This feature of pemphigus vulgaris can be used in making a diagnosis based on the identification of these rounded cells (Tzanck cells) in an exfoliative cytologic preparation. A mild-to-moderate chronic inflammatory cell infiltrate is usually seen in the underlying connective tissue.

The diagnosis of pemphigus vulgaris should be confirmed by direct immunofluorescence examination of fresh perilesional tissue or tissue submitted in Michel's solution. With this procedure, antibodies (usually IgG or IgM) and complement components (usually C3) can be demonstrated in the intercellular spaces between the epithelial cells in almost all patients with this disease.

Indirect immunofluorescence is also typically positive in 80% to 90% of cases, demonstrating the presence of circulating autoantibodies in the patient's serum.







Treatment:

Pemphigus is a systemic disease; therefore, treatment consists primarily of systemic corticosteroids (usually prednisone), often in combination with other immunosuppressive drugs (so-called steroid-sparing agents) such as azathioprine.

The most common approach is to use relatively high doses of systemic corticosteroids initially to clear the lesions, and then attempt to maintain the patient on as low a dose of corticosteroids as is necessary to control the condition. The use of topical corticosteroids in the management of oral lesions is also common with low dose of systemic corticosteroid .

❖ Mucous Membrane Pemphigoid (Cicatricial pemphigoid; benign mucous membrane pemphigoid)

Mucous membrane pemphigoid represents a group of chronic, blistering، mucocutaneous autoimmune diseases in which tissue-bound autoantibodies are directed against one or more components of the basement membrane.

Clinical Features:

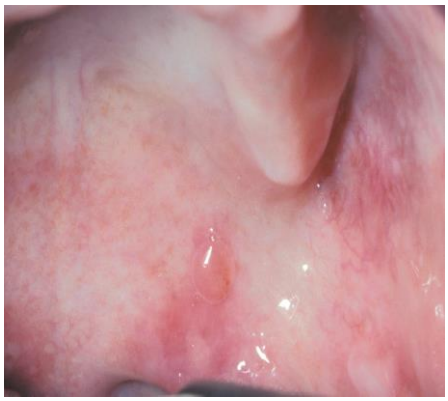
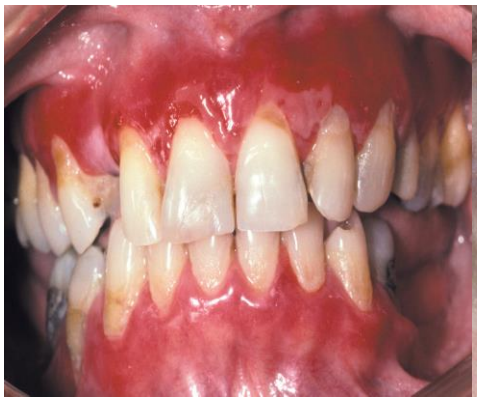
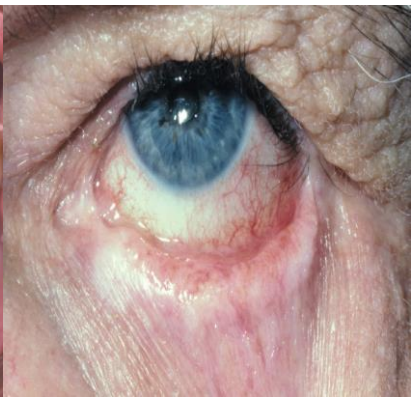
Mucous membrane pemphigoid usually affects older adults، with an average age of 50 to 60 years at the onset of disease. Females are affected more frequently than males. Oral lesions are seen in most patients, but other sites، such as conjunctival, nasal, esophageal, laryngeal, and vaginal mucosa, as well as the skin may be involved.

The oral lesions of pemphigoid begin as either vesicles or bullae that may occasionally be identified clinically. In contrast, patients with pemphigus rarely display such blisters. Eventually, the oral blisters rupture, leaving large, superficial, ulcerated, and denuded areas of mucosa . The ulcerated lesions are usually painful and persist for weeks to months if untreated.

Often this process is seen diffusely throughout the mouth, but it may be limited to certain areas, especially the gingiva . Gingival involvement produces a clinical reaction pattern termed desquamative gingivitis.

The most significant complication of mucous membrane pemphigoid, however, is ocular involvement. The earliest change is subconjunctival fibrosis. As the disease progresses, the conjunctiva becomes inflamed and eroded. Attempts at healing lead to scarring .

Other mucosal sites may also be involved and cause considerable difficulty for the patient.

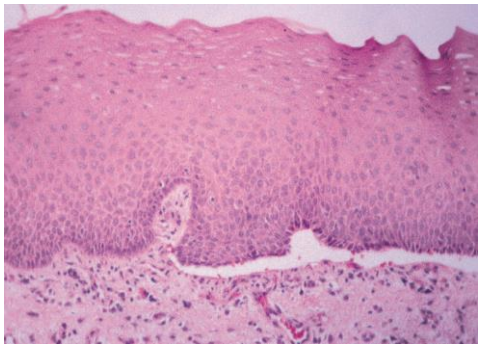




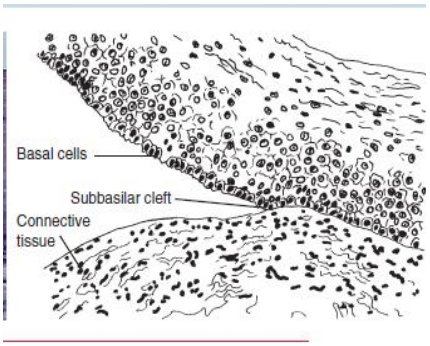
Histopathologic Features:

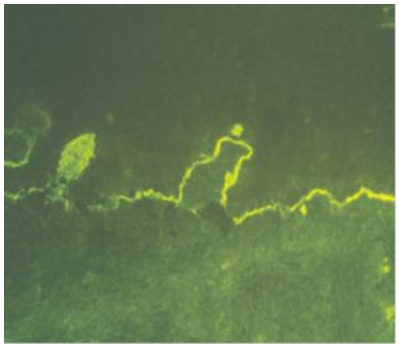
Biopsy of perilesional mucosa shows a split between the surface epithelium and the underlying connective tissue in the region of the basement membrane . A mild chronic inflammatory cell infiltrate is present in the superficial submucosa.

Direct immunofluorescence studies show a continuous linear band of immunoreactants at the basement membrane zone in nearly 90% of affected patients .

The immune deposits consist primarily of IgG and C3 .







Treatment:

In fact, there is no single good therapy for every patient; treatment must be individualized, depending on lesional distribution، disease activity, and therapeutic response.

Topical Agents use If only oral lesions are present, such as topical corticosteroids . Once control is achieved, the applications can be discontinued.

Patients with only gingival lesions often benefit from good oral hygiene measures. As an additional aid in treating gingival lesions, a flexible mouth guard may be fabricated to use as a carrier for the corticosteroid medication.

Systemic Agents used If topical corticosteroids are unsuccessful. Dapsone, can be used to treat patients with mild-to-moderate involvement by mucous membrane pemphigoid. Another alternative systemic therapy that may be used for patients with less severe disease is tetracycline or minocycline and niacinamide (nicotinamide).

Some studies have suggested that treatment with intravenous (IV) human immunoglobulin.

❖ BULLOUS PEMPHIGOID

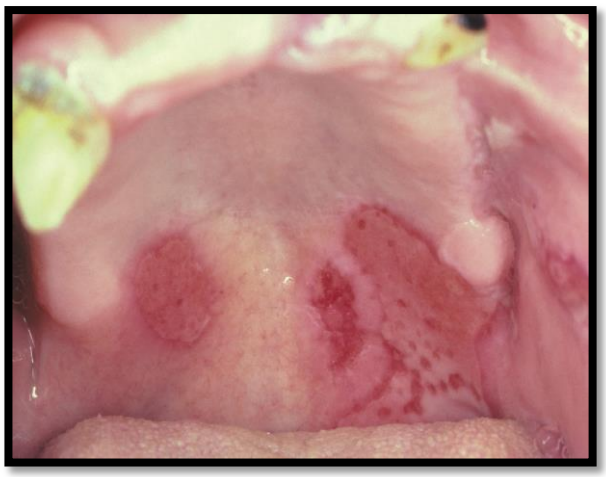
Bullous pemphigoid is the most common of the autoimmune blistering conditions. The disease is characterized by the production of autoantibodies directed against components of the basement membrane. In many respects, bullous pemphigoid resembles mucous membrane pemphigoid, but most investigators note
that there are enough differences to consider these diseases as distinct but related entities. One significant difference is that the clinical course in patients with bullous pemphigoid is usually characterized by periods of remission followed by relapse, whereas the course in patients with mucous membrane pemphigoid is usually protracted and progressive.

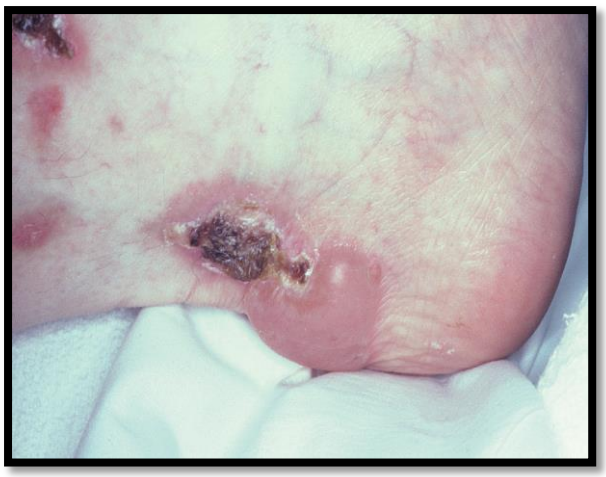
Clinical Features:

Bullous pemphigoid typically develops in older people؛ most patients are between 75 and 80 years of age. No sex or racial predilection is generally reported. Pruritus is often an early symptom. This is followed by the development of multiple, tense bullae on either normal or

erythematous skin . These lesions eventually rupture after several days, causing a superficial crust to form. Eventually, healing takes place without scarring.

Oral mucosal involvement is uncommon, with approximately 10% to 20% of patients being affected. The oral lesions, like the skin lesions, begin as bullae, but they tend to rupture sooner, probably as a result of the constant low grade trauma to which the oral mucosa is subjected. Large، shallow ulcerations with smooth, distinct margins are present after the bullae rupture .





Histopathologic Features:

Microscopic examination of tissue obtained from the perilesional margin of a bulla shows separation of the epithelium from the connective tissue at the basement membrane zone, resulting in a subepithelial separation. Modest numbers of both acute and chronic inflammatory cells are typically seen in the lesional area, and the presence of eosinophils within the bulla itself is characteristic.

Direct immunofluorescence studies show a continuous linear band of immunoreactants, usually IgG and C3, localized to the basement membrane zone in 90% to 100% of affected patients. These antibodies bind to proteins associated with hemidesmosomes, structures that bind the basal cell layer of the epithelium to the basement membrane and the underlying connective tissue.

In addition to the tissue-bound autoantibodies, 50% to 90% of the patients also have circulating autoantibodies in the serum, producing an indirect immunofluorescent pattern that is identical to that of the direct immunofluorescence.

Treatment :

Treatment of patients with mild or localized bullous pemphigoid consists of application of one of the stronger topical corticosteroid preparations.

Management of the patient with moderate-to-severe, widespread bullous pemphigoid daily doses of systemic prednisone.

If the lesions do not respond to prednisone alone, then another immunosuppressive agent (such as, azathioprine, methotrexate, or mycophenolate mofetil) may be added to the regimen.

Dapsone, a sulfa derivative, may be used as an alternative therapeutic agent, and tetracycline and niacinamide therapy is reported to be effective for some patients.

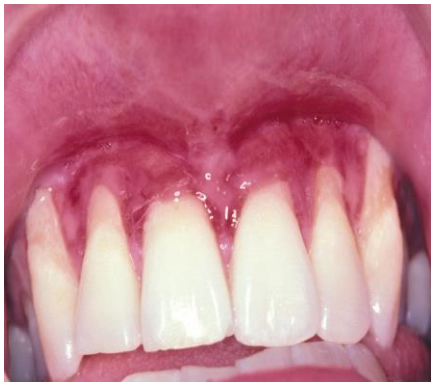
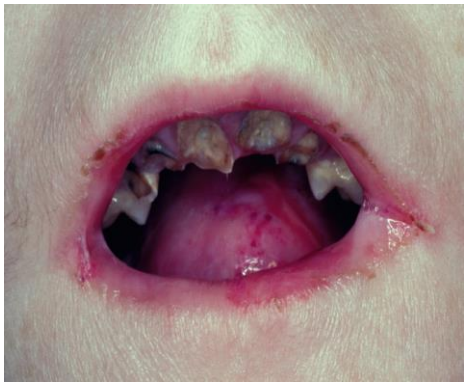
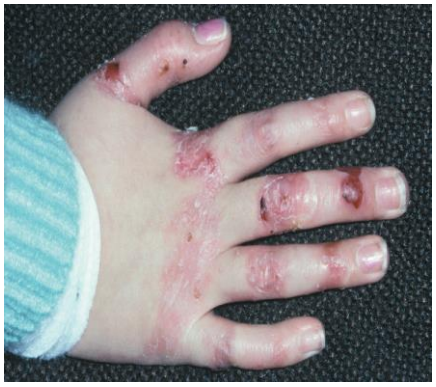
❖ EPIDERMOLYSIS BULLOSA

Epidermolysis bullosa is a general term that encompasses one acquired
And as many as 20 genetic or hereditary varieties (dystrophic,junctional، simplex) of diseases that basically are characterized by the formation of blisters at sites of minor trauma.

Clinical features:

The initial lesions in all subtypes of epidermolysis bullosa are vesicles or bullae, which are seen early in life and develop on areas exposed to low-grade, chronic trauma, such as the knuckles or knees . The bullae rupture, resulting in erosions or ulcerations that ultimately heal with scarring. In the process, appendages such as fingernails may be lost.

The oral manifestations are typically mild in Dominant Dystrophic Types , with some gingival erythema and tenderness. Gingival recession and reduction in the depth of the buccal vestibule may be observed . In Recessive Dystrophic the oral problems are no less severe. Bulla and vesicle formation is induced by virtually any food having some degree of texture. Even with a soft diet, the repeated cycles of scarring often result in microstomia .

Treatment :

Treatment of epidermolysis bullosa varies with the type. For milder cases, no treatment just avoidance of trauma . Sterile drainage of larger blisters and the use of topical antibiotics are often indicated in these situations.

For the more severe cases, intensive management with oral antibiotics may be necessary if cellulitis develops .Treatment also include supportive measures and chemotherapeutic agents, corticosteroids ,vitamin E phenytoin and immunosuppressive agents.